

REMARKS

Claims 56-57, 59-60 and 63-73 are pending. Claims 58 and 61-62 have been cancelled. Claims 56 and 67 have been amended to include the limitations of claim 58. Applicants submit that no new matter has been added.

The claims of the application stand variously rejected. Claims 56-60 and 63-71 stand rejected under judicially created obviousness-type double patenting over U.S. Patent No. 5,763,429. Claims 56-58, 61 and 67-71 stand rejected under 35 USC § 102(a) over U.S. Patent No. 5,547,947 issued to Dore et al. (hereinafter "Dore"). Claims 72-73 stand rejected under 35 USC § 103(a) as being obvious over Dore in view of U.S. Patent No. 5,300,687 issued to Schwender et al. (hereinafter "Schwender"). Claim 62 stands rejected under 35 USC § 103(a) as being obvious over Dore in view of U.S. Patent No. 4,391,802 issued to Suda et al. (hereinafter "Suda"). Applicants traverse these rejections for at least the following reasons.

Obviousness-type double patenting rejection

Claims 56-60 and 63-71 stand rejected under judicially created obviousness-type double patenting over U.S. Patent No. 5,763,429. Applicants submit herewith a terminal disclaimer in compliance with 37 CFR § 1.321(c) to U.S. Patent No. 5,763,429. Applicants respectfully request that the rejection to claims 56-60 and 63-71 over U.S. Patent No. 5,763,429 be withdrawn.

Rejections under 35 USC § 102(a) over Dore

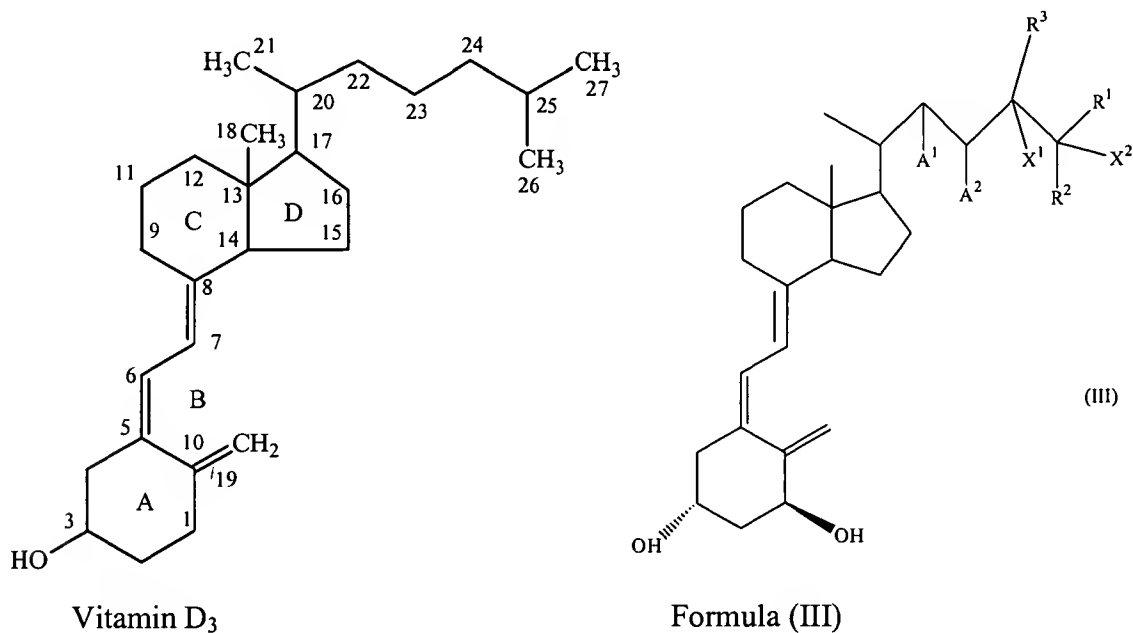
Claims 56-58, 61 and 67-71 stand rejected under 35 USC § 102(a) over U.S. Patent No. 5,547,947 issued to Dore et al. (hereinafter "Dore"). The Manual of Patent Examining Procedure "MPEP" states that, in order to anticipate a claim, a reference must teach every element of the claim:

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*,

868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).” See MPEP § 2131.

Applicants submit that the Dore reference fails to disclose each and every element of claims 56-57, 61 and 67-71 as amended.

Claim 56, upon which claims 57, 59-60 and 63-66 depend from directly or indirectly, and claim 67, upon which claims 68-73 depend from directly or indirectly, have been amended to be limited to vitamin D compounds of formula (III). The compounds of formula III are limited to vitamin D₂ and vitamin D₄ compounds and, therefore, do not include any vitamin D₃ compounds. Vitamin D₃ compounds (as shown below) contain no substituted carbon based groups off of the 24th carbon



In contrast, formula (III) in claims 56 and 67 as amended, contain the limitation that “R³ is lower alkyl, lower alkenyl, lower fluoroalkyl, lower fluoroalkenyl, O-lower alkyl, O-lower alkenyl, O-lower acyl, O-aromatic acyl or lower cycloalkyl”, and that “A¹ and A² each are hydrogen or together represent a carbon-carbon bond, thus forming a double bond between C-22 and C-23”. When A¹ and A² each are hydrogen, the compound is a vitamin D₄ composition, and

when A¹ and A² together represent a carbon-carbon bond, the compound is a vitamin D₂ composition.

The Dore reference is directed towards a method of inducing inhibition or loss of cell proliferation in solid tumors utilizing a Vitamin D₃ analog. The Dore reference contains no teaching of the use of any vitamin D₂ or D₄ analog to inhibit the hyperproliferation of cells. As the Dore reference fails to teach all of the elements of claims 56-57, 61 and 67-71 as amended, the reference fails to anticipate the claims. Applicants respectfully request that the Examiner withdraw the rejections to the claims based on this ground.

Rejections under 35 USC 103(a) over Dore in view of Schwender

Claims 72-73 stand rejected under 35 USC § 103(a) as being obvious over Dore in view Schwender. The MPEP states that:

“To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 165 USPQ 494, 496 (CCPA 1970).” See MPEP § 2141.03.

Applicants respectfully submit that the Office Action has failed to put forth a *prima facie* case of obviousness, as the combined references of Dore and Schwender, alone or in combination, fail to teach or suggest all of the limitations of claims 72-73 as amended.

Claims 72 and 73 each depend from claim 67 which has been amended to be limited to vitamin D compositions of formula (III). The compositions of formula (III) are limited to vitamin D₂ and D₄ compositions.

As discussed above, the Dore reference only discloses the use of vitamin D₃ analogs for treating hyperproliferation, and contains no teaching or suggestion of the use of any vitamin D₂

or D₄ composition. The Schwender patent contains no teaching or suggestion of the use of any vitamin D compound to inhibit hyperproliferation, let alone a vitamin D₂ or D₄ compound.

As indicated in the specification of the present application, previous studies of vitamin D compounds and cancer treatment have focused exclusively on vitamin D₃ compounds. Even though these compounds may indeed be highly effective in promoting differentiation in malignant cells in culture, their practical use in differentiation therapy as anticancer agents is severely limited because of their equally high potency as agents affecting calcium metabolism. At the levels required *in vivo* for effective use as, for example, antileukemic agents, these same compounds can induce markedly elevated and potentially dangerous blood calcium levels by virtue of their inherent calcemic activity. That is, the clinical use of 1,25-dihydroxyvitamin D₃ and other vitamin D₃ analogues as anticancer agents is precluded, or severely limited, by the risk of hypercalcemia. This indicates a need for compounds with greater specific activity and selectivity of action, i.e., vitamin D compounds with antiproliferative and differentiating effects but which have less calcemic activity.

In addition to the risk of hypercalcemia associated with clinical use of certain vitamin D compounds that are potent stimulators of intestinal calcium absorption, hypercalcemia has now also been specifically associated with malignancy. Such malignancy associated hypercalcemia (MAH) is often a major contributor to morbidity and complicates clinical management of the malignancy. Parathyroid hormone related protein (PTHrP) is one of the main causative substances of such hypercalcemia, and is overproduced by malignant cells. PTHrP is closely related to parathyroid hormone (PTH) and binds to the same receptor as PTH as well as other receptors. 1,25-dihydroxyvitamin D₃ has been found to repress the transcription of the PTHrP gene in cells; however, the 1,25-dihydroxyvitamin D₃ compounds themselves increase serum calcium levels.

The Dore reference contains no teaching or suggestion that any vitamin D₂ or D₄ compounds would be useful in treating hyperproliferation, let alone that they could be used without inducing hypercalcemia.

The Dore and Schwender references, alone or in combination, fail to teach or suggest all of the limitations of claims 72-73. Applicants therefore submit that a *prima facie* case of

obviousness has not been made with respect to claims 72-73, and respectfully request that the rejection to the claims be withdrawn.

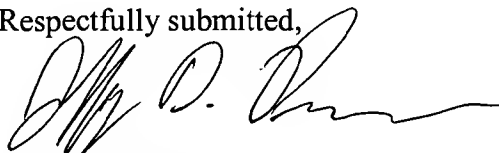
Rejections under 35 USC 103(a) over Dore in view of Suda

Claim 62 stands rejected under 35 USC § 103(a) as being obvious over Dore in view of Suda. This rejection has been rendered moot by the cancellation of claim 62.

SUMMARY

Based on the foregoing, Applicants respectfully submit that the present application is in condition for allowance, and a favorable action thereon is respectfully requested. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Jeffrey D. Peterson

Reg. No. 49,038

Docket No.: 017620-9335
Michael Best & Friedrich LLP
One South Pinckney Street
P. O. Box 1806
Madison, WI 53701-1806
608.257.3501
Q:\client\017620\9335\B0652952.1